

# LETTERS *to the Editor*

## Aspirin and Salicylic Acid, et al.

*To the Editor:* The statement of Babb and Wilbur (Calif. Med. 110:440, May 1969) "In our experience, aspirin is a common and often overlooked cause of gastrointestinal bleeding" can be extended to other types of unexplained bleeding, but their assertion that: "Since we know of no accurate method of predicting 'susceptibility,' we must consider aspirin potentially dangerous to anyone" is incorrect. The diagnostic procedure, the aspirin tolerance test,<sup>1</sup> not only reliably detects subjects that are sensitive to aspirin, but furnishes information that throws light on the action of this drug.

Unfortunately knowledge concerning the salicylates is still in a confused state as clearly shown in an excerpt of Engleman (Calif. Med. 110:422, May 1969) in which it is stated: "The drugs of choice—the drug that is recommended almost universally for rheumatoid arthritis—is the salicylate." Equally puzzling are various statements occurring in the Medical Staff Conference: The Clinical Pharmacology of Salicylates (Smith, L. H. and Melmon, K. L., Rowland, M. and Morrelli, H., Calif. Med. 110:410, May 1969). One of these is "Aspirin is hardly new to clinical medicine with regard either to use as a drug or knowledge of the

pharmacological activity. What is known of this activity had been described almost completely before the Christian era." And "Thus aspirin is one of the oldest compounds, senior to quinine colchicine and digitalis." Obviously the confusion stems from the failure to differentiate aspirin from salicylic acid and its various derivatives.

Aspirin is the trade name for acetylsalicylic acid whereas the term salicylates in a strictly chemical sense are the various salts of salicylic acid. Thus, such a drug as salicylamide is not a salicylate. Contrary to the statements made in this conference, salicylic acid is not commonly found in plants whereas the salicyl radical is widely distributed in various species of plants, notably as the glucoside salicin in which the aglycone is ortho-oxybenzyl alcohol. Methyl salicylate, or oil of wintergreen, is one of the few examples of salicylic acid occurring in plants. Aspirin is a synthetic product first prepared in 1853 but not introduced into medicine until 1899. It does not occur in plants and was neither known nor used by any physician before the turn of the century until Felix Hoffmann employed it in treating his father, who had rheumatoid arthritis.

This critical analysis may appear *a priori* as academic, but actually it is of vital importance because aspirin is the most widely used drug of all time and the amount consumed yearly is phenomenal. Sodium salicylate was recognized as an antipyretic and anti-inflammatory agent, particularly efficacious in the treatment of rheumatic fever, long before aspirin was introduced into therapy. Acetylation of salicylic acid to form aspirin produces a new drug with definitely increased analgesic potency, which has led to the wide replacement of sodium salicylate. Unfortunately acetylation also introduced other properties, particularly the effect on hemostasis which is responsible for the bleeding problem.

Acetylsalicylic acid will increase the Duke bleeding time in many presumably normal subjects and significantly in patients with the Minot-von Willebrand syndrome.<sup>1</sup> Such an effect is not produced by sodium salicylate. Since the bleeding time is a sensitive index of the bleeding tendency, no surgical patient should be given aspirin unless his aspirin tolerance test has been checked.<sup>2</sup> This applies particularly to minor surgical procedures such as tonsillectomy and tooth extraction. Aspirin is contraindicated in hemophilia. It is quite likely that this drug plays an important part in many of the crippling hemarthroses.

Though aspirin has undesirable qualities, it remains one of the most effective analgesic agents, and for all except a small group of subjects it remains a safe drug and this can be assured by the aspirin tolerance test.

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#### REFERENCES

1. Quick, A. J.: Salicylates and bleeding: The aspirin tolerance test, *Amer. J. Med. Sci.*, 252:265, Sept. 1966.
2. Quick, A. J.: Hemostasis in surgical procedures, *Surg., Gynec. & Obstet.*, 128:523, Mar. 1969.

*To the Editor:* In response to the interesting note of Dr. Armand J. Quick, Marquette School of Medicine, Inc., Milwaukee, I think that the following points made in relation to articles recently published in CALIFORNIA MEDICINE are reasonable. While it would be pleasant to feel that an aspirin tolerance test could well predict the most reasonable doses of the drug to be used in any given individual and that careful administration of the drug would then result in decreased bleeding tendency, it does appear that (1) the pharmacology of acetylsalicylic acid as stated by Dr. Quick will produce the bleeding abnormalities as part and parcel of its other pharmacologic effects; (2) the practical fact in the day to day management of patients is that the tolerance test is not commonly used. This does not excuse the medical community for ignoring a test of usefulness, but it must be borne in mind that acetylsalicylic acid is a proprietary drug in many instances not entirely

under the control of physicians. The relative indiscriminate distribution of the drug, i.e. the amount which is consumed as over-the-counter preparations is going to remain uncontrolled as long as the FDA allows free use of a potentially dangerous compound. In addition, recent data seems to indicate that to some degree this bleeding seems inevitable.

Both the articles by Engelman, et al and Melmon, et al used terminology which was imprecise, but consistent with common clinical phraseology of the drug. The physicians' expression of desirability of aspirin and the universal and preferential use of aspirin for the treatment of rheumatoid arthritis can not be contested. When one considers the alternatives to the use of acetylsalicylic acid, aspirin becomes most certainly the one drug with the highest benefit:risk ratio. Likewise, the authors apologize for the imprecise use of the term *aspirin* for the broader term *salicylates*. Dr. Quick is correct in his chemical classification. Aspirin is only one of many salicylates. His description of the distribution of the salicyl radical in plants is more correct than our own. However, the pharmacology of those compounds containing the salicyl radical seems related to sodium salicylate which is of course close to acetylsalicylic acid. References quoted in the "clinical pharmacology" article contain the details of the history of the development of the synthesis, pharmacologic understanding and use of aspirin which were in part recorded by Dr. Quick. In the United States, our reading of the literature brings us to the view that acetylsalicylic acid has been clinically selected, not so much because of more pronounced anti-inflammatory or analgesic effect above other salicylates but because others have agreed with Felix Hoffman, who when giving acetylsalicylic acid to his father, found the acetyl derivative of salicylic acid rather than the sodium salts of the acid much less irritating to the gastrointestinal tract.

Finally, Dr. Quick's point is well taken in the possible clinical misuse of aspirin, and it is of interest that he pointed out that such misuse might cause critical complications in some patients with leukemia. We agree that this is a distinct possibility. A careful study documenting the later statement made by Dr. Quick would be most helpful to many clinicians.

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